Severity and Prognosis of Acute Human Immunodeficiency Virus Type 1 Illness: A Dose-Response Relationship

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This study examined the relationship between the severity of acute human immunodeficiency virus type 1 (HIV-1) illness and disease progression and death. The population included 218 patients with acute HIV-1 illness and 41 asymptomatic patients who underwent HIV-1 seroconversion; the patients were followed up prospectively. We analyzed progression to Centers for Disease Control and Prevention clinical categories B and C (AIDS-defining conditions) and death according to an additive clinical score (CS) based on six predictive clinical features at the time of acute HIV-1 infection. Compared with patients with a CS of 0 (asymptomatic patients), those with a CS of 3–4 and 5–6 had faster progression to category B disease (adjusted hazard ratio [HR], 1.39; 95% confidence interval [CI], 1.01–1.92; and HR, 1.80; 95% CI, 1.34–2.40; respectively); those with a CS of 5–6 had faster progression to category C disease (HR, 1.37; 95% CI, 1.01–1.89) and death (HR, 2.05; 95% CI, 1.27–3.32). Thus, the number of symptoms and signs at the time of acute HIV-1 illness affects disease progression and survival, even in symptomatic patients who have undergone seroconversion.

The duration and the severity of acute HIV-1 illness have been associated with a more rapid disease progression [1–6] and were associated with shorter survival in one study [6]. However, the usual classification of patients who seroconverted as symptomatic or asymptomatic does not adequately explore the predictive value of different symptoms and signs in symptomatic patients who seroconverted.

According to the Centers of Disease Control and Prevention (CDC) [7], the first clinical event of category B is an HIV-1-related event, mostly consisting of oral lesions, that is associated with the subsequent risk of an event of category C (AIDS-defining conditions) and death [8–10].

We were thus interested in exploring whether a score representing a gradient of clinical severity of acute HIV-1 disease could identify patients at higher risk of progression. More specifically, the objectives of this study were to identify symptoms and signs reported at the time of acute HIV-1 infection that are associated with rapid progression to the first clinical event of category B and to estimate the hazard ratio (HR) for AIDS, defined as the first clinical event of category C and death in terms of the number of symptoms and signs at the time of acute HIV-1 infection.

Methods

Study Population

We investigated 259 newly HIV-1-infected persons enrolled in four prospective studies of the incidence of HIV-1 disease that were performed between 1985 and 1994 and had similar standardized biannual follow-ups. Two cohorts were coordinated by the National Centre in HIV Epidemiology and Clinical Research in Sydney, New South Wales, Australia, and two cohorts were coordinated in Geneva. The Australian cohorts involved 171 patients, mostly homosexual men at risk of HIV infection, who have been extensively described elsewhere [11–13]. The European cohorts consisted of 88 patients of both genders who had various risk factors for acquisition of HIV infection and were enrolled in the Swiss HIV Cohort Study in Geneva [14] or in a placebo-controlled trial of zidovudine during primary HIV-1 infection [15].

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Informed consent was obtained from all patients enrolled in the different cohorts.

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Biological and Clinical Inclusion Criteria

Symptomatic patients. Acute HIV-1 infection in 218 patients was confirmed by the following criteria: (1) the presence of p24 antigen in blood with negative or indeterminate antibodies to HIV by ELISA (135 patients [62%]); (2) two bands on a western blot, one of which corresponded to the *env* gene (glycoprotein [gp] 160, gp 120, or gp 41) with negative or indeterminate antibodies to HIV by ELISA (18 [8%]); or (3) a negative HIV-1 ELISA followed by a positive HIV-1 ELISA within 1 year (mean, 140.0 days) (65 [30%]). The diagnosis of HIV-1 infection was confirmed by western blotting of follow-up blood samples from all patients included in this study. Their symptoms and signs have been extensively reported [13], and only those occurring in >10% of patients were analyzed here.

Asymptomatic patients. Forty-one asymptomatic patients had a negative HIV-1 ELISA followed by a positive HIV-1 ELISA within 1 year (mean, 180.0 days) (criterion 3). They were enrolled in the cohorts at the same time as the symptomatic patients, and their asymptomatic status was assessed according to self-report and was confirmed by examination of each patient's medical record.

End points. The end points considered in this study were clinical events exclusively. The clinical end points were the first clinical event of category B (AIDS excluded), the first clinical event of category C (or an AIDS-defining condition), as defined by the 1992 criteria of the CDC [7], and death. The diagnoses and dates of HIV-1-related events were confirmed by examination of medical records and were also cross-checked against the database of the Swiss HIV Cohort Study in Geneva and the AIDS registry of the National Centre in HIV Epidemiology and Clinical Research in Sydney [16]. We did not use the CD4 cell count as a diagnostic criterion for category B and category C outcomes. Because some clinical features of acute HIV-1 infection could be similar to clinical end points (i.e., oral candidiasis or diarrhea), we confirmed that all acute signs and symptoms used in the prognostic analysis (see below) had resolved at the end of the acute stage of HIV-1 infection. HIV-1-related deaths were confirmed from medical records and the autopsy reports if available.

Statistical Analysis

Disease progression was defined by occurrence of the first category B disease, the first category C disease, and HIV-1-related death. Eight patients who died of causes not considered HIV-1-related (4 overdoses, 2 suicides, 1 acute myocardial infarction, and 1 murder) were censored for survival analysis at the time of death.

Survival analysis started from time 0, defined as the date of documented acute HIV-1 infection (criterion 1 or 2) or the midpoint between the last negative and the first positive HIV-1 screening test (criterion 3). Survival time to category B disease, category C disease, and HIV-1-related death was measured from time 0 to each outcome or censored at the date that the patient was last confirmed to be alive and not to have reached any end point at study termination (1 June 1995). The survival curves did not differ by time 0 definitions among patients with acute HIV-1 illness.

Time to category B disease was estimated by the Kaplan-Meier method and compared by the generalized Wilcoxon test (which gives more weight to early events [17]) after stratification of the presence or absence of each symptom and sign at the time of acute HIV-1 illness. Proportional hazards models [18] were fitted to estimate the unadjusted and adjusted HR of category B disease after selection of symptoms and signs from the univariate analysis and assumption of risk proportionality. The multivariate analyses were always adjusted by center (Geneva vs. Sydney) as a confounder to account for variations that could have occurred between the centers, such as the sex ratio, the proportion of patients per risk factor for HIV-1 infection, and potential differences of frequency of symptoms and signs reported.

To explore a potential dose-effect relationship between the number of symptoms and signs and disease progression, we created an additive clinical score (CS) with variables individually associated with progression to category B disease at a statistical level of ⩽.10 that were determined by the generalized Wilcoxon test. (Pharyngitis was included because of its high prevalence and a P value of .11.) The prognostic value of the symptoms and signs included in the CS was also confirmed by univariate proportional hazards models. The CS consisted of the sum of values for each variable (0 for absent or not reported and 1 for present). The adjusted HR for category B disease, category C disease, and death by CS was estimated by using the proportional hazards models with asymptomatic patients as the reference group (CS, 0; HR, 1.0).

To estimate a synergistic effect on disease progression between the presence of clinical features and their duration, we tested the interaction term (CS × duration of symptoms) by using the proportional hazards model.

All P values were two-sided and considered significant if <.05.

Results

The patients were mostly men (93%), and the probable mode of HIV-1 infection was homosexual or bisexual contact in 79% of cases. The mean age of the patients ± SD was 31.7 ± 7.7 years, and the mean duration of acute HIV-1 illness ± SD was 25.1 ± 22.3 days. The conditions of 81 (31%), 63 (24%), and 54 (21%) of the patients progressed to category B disease, category C disease, and death, respectively; these categories were not mutually exclusive. The median follow-up for the entire cohort was 3.2 years (range, 0.12–10.6 years). The me-

dian times to category B disease, category C disease, and death were 6.1 years (95% CI, 5.1–7.1), 7.3 years (95% CI, 6.7–8.0), and 8.6 years (95% CI, 7.3–9.8), respectively.

The median time of progression to category B disease according to symptoms and signs at the time of acute HIV-1 infection is shown in table 1. Oral candidiasis, which occurred in 37 patients (14%), was the strongest predictor, with a median time to disease of 3.9 years compared with 6.6 years for patients without this condition ($P = .0002$) and with an adjusted HR of 2.88 (95% CI, 1.47–5.63; $P = .002$); the HR was adjusted for center (0.50; 95% CI, 0.30–0.90), age (1.01; 95% CI, 0.98–1.05), duration of acute HIV-1 illness (0.99; 95% CI, 0.97–1.00), year of infection (1.19; 95% CI, 0.73–1.92), zidovudine administration at the time of acute HIV-1 infection (0.62; 95% CI, 0.31–1.27), and other symptoms and signs. Lethargy was also associated with progression to category B disease, with an adjusted HR of 1.84 (95% CI, 1.02–3.32; $P = .04$).

Table 1. Symptoms and signs at the time of acute HIV-1 illness in 259 patients that were associated with the first category B disease.

Symptom or sign*	No. of patients	Median time† (y) to the first category B disease (95% CI)	*P* value‡
Diarrhea			
No	209	6.4 (5.7–7.0)	
Yes	50	4.6 (3.0–6.1)	.05
Abdominal pain			
No	217	6.2 (5.3–7.0)	
Yes	42	4.2 (1.1–7.2)	.01
Fever (temperature, ⩾38°C)			
No	91	6.8 (5.8–7.7)	
Yes	168	5.1 (4.0–6.2)	.03
Night sweats			
No	211	6.1 (5.7–6.7)	
Yes	48	4.3 (3.0–5.7)	.05
Lethargy			
No	116	7.0 (6.1–8.0)	
Yes	143	5.1 (4.2–6.0)	.008
Skin rash			
No	136	6.8 (5.8–7.8)	
Yes	123	4.6 (3.2–5.9)	.004
Pharyngitis or sore throat			
No	163	6.6 (5.6–7.2)	
Yes	96	5.1 (4.6–5.6)	.11
Odynophagia			
No	198	6.2 (5.6–6.7)	
Yes	61	5.1 (3.1–7.1)	.01
Oral candidiasis			
No	222	6.6 (6.0–7.1)	
Yes	37	3.9 (2.2–5.5)	.0002
None of the above symptoms	52	7.2 (6.3–8.1)	
One or more of the above symptoms	207	5.5 (4.5–6.4)	.04

* The symptoms and signs reported here were listed extensively in [13]. In the present study, the symptoms and signs with the highest association with the first category B disease are reported (results for other symptoms and signs are available from the corresponding author).

† Kaplan-Meier method.

‡ Generalized Wilcoxon test.

The symptoms and signs reported in table 1 were candidate predictors for the additive CS. The most parsimoniously discriminating CS included fever (temperature, ⩾38°C), skin rash, lethargy, oral candidiasis, pharyngitis or sore throat, and diarrhea. The univariate HRs for the symptoms and signs of the first category B disease were as follows: fever, 1.86 (95% CI, 1.18–2.95); skin rash, 2.0 (95% CI, 1.28–3.12); lethargy, 2.04 (95% CI, 1.30–3.21); oral candidiasis, 2.60 (95% CI, 1.48–4.60); pharyngitis or sore throat, 1.44 (95% CI, 0.91–2.25); and diarrhea, 1.38 (95% CI, 0.83–2.31). The CS ranged from 0 to 6 and was stratified as 0, 1–2, 3–4, and 5–6 (from absence to high severity). The adjusted HR for each outcome by CS strata is shown in table 2. Patients with a CS of moderate (3–4) to high (5–6) severity had a higher risk of progression to category B disease, but only patients with a CS of high severity had a higher risk of progression to category C disease and death.

The risk of progression to category B disease, category C disease, and death at 3, 5, and 7 years per CS strata is reported in table 3.

For our study population, the interaction term (CS × duration of symptoms) was not statistically associated with a faster progression to the first category B disease (HR, 0.98; 95% CI, 0.95–1.02), the first category C disease (HR, 1.0; 95% CI, 0.95–1.05), or death (HR, 0.98; 95% CI, 0.92–1.05).

Discussion

Our aim was to investigate the association between the type, number, and duration of symptoms and signs reported at the time of acute HIV-1 illness and disease progression and survival.

Specific features of acute HIV-1 illness previously associated with disease progression were rash and fever [2, 5], possibly because these features were easy to detect and also because these studies were done early in the AIDS epidemic (when descriptions of acute HIV-1 illness were less detailed). These findings were not confirmed in the present study because of the high correlation between symptoms; we found that oral candidiasis was the strongest predictor of disease progression after adjustment.

Our results suggest a dose-response relationship between the number of symptoms and signs at the time of acute infection and the prognosis, since the highest rate of progression and death was found among patients with the highest CS. A significant HR for category B disease was observed for those patients

Table 2. Adjusted HRs for category B disease, category C disease, and death by clinical score of the severity of acute HIV-1 disease in 259 patients.

Clinical score	Severity	No. of patients	HR of category B disease			HR of category C disease			HR of death		
			HR*[†]	95% CI	*P* value	HR[‡]	95% CI	*P* value	HR[§]	95% CI	*P* value
0		52	1.00			1.00			1.00		
1–2	Low	77	1.26	0.66–2.38	.47	0.95	0.47–1.89	.98	1.34	0.57–3.15	.49
3–4	Moderate	102	1.39	1.01–1.92	.03	1.10	0.78–1.55	.58	1.34	0.93–1.93	.11
5–6	High	28	1.80	1.34–2.40	.0001	1.37	1.01–1.89	.04	2.05	1.27–3.32	.003

NOTE. HR = hazard ratio.

* Each stratum was compared with the reference stratum (clinical score = 0).

[†] The value of the likelihood was (−2 log likelihood) 712.078 with 5 df ($P = .001$). The model was adjusted for center (Geneva vs. Sydney, New South Wales, Australia) (HR, 0.5; 95% CI, 0.30–0.94); age as a continuous variable (HR, 1.0; 95% CI, 0.97–1.03); year of infection stratified as until 1987 ($n = 86$), from 1988 to 1991 ($n = 65$), and from 1992 ($n = 108$) (HR, 1.05; 95% CI, 0.68–1.64); and zidovudine administration at the time of acute HIV-1 disease ($n = 68$) (HR, 0.63; 95% CI, 0.32–1.24).

[‡] The value of the likelihood was (−2 log likelihood) 488.120 with 5 df ($P < .0001$). The model was adjusted for center (HR, 0.60; 95% CI, 0.21–1.50), age (HR, 1.0; 95% CI, 0.97–1.04), year of infection (HR, 1.63; 95% CI, 0.85–3.10), and zidovudine administration before category C disease ($n = 43$) (HR, 7.1; 95% CI, 3.9–12.8).

[§] The value of the likelihood was (−2 log likelihood) 383.328 with 6 df ($P = .0001$). The model was adjusted for center (HR, 0.58; 95% CI, 0.13–2.58), age (HR, 1.01; 95% CI, 0.97–1.06), year of infection (HR, 0.92; 95% CI, 0.38–2.21), zidovudine use at any time ($n = 89$) (HR, 1.34; 95% CI, 0.73–2.45), and use of secondary prophylaxis for *Pneumocystis carinii* pneumonia ($n = 15$) (HR, 4.89; 95% CI, 2.40–9.97).

with at least three symptoms or signs. For category C disease and death, a significant HR was observed for those patients with at least five symptoms or signs, thus suggesting that the most severe acute illnesses only predict advanced disease. The HR observed between patients in extreme categories (0 vs. 5–6) was less than HRs observed in previous studies [1, 2, 4, 5]. This finding could be explained by a different study population, but it could also be explained by previous investigators having considered all symptomatic patients in the same group [4, 5] and by different adjustments on confounders. Perhaps most important, 47% of our patients were infected after 1992, which means that they were more likely to receive antiretroviral therapy (which could decrease the prognostic impact of the severity of acute HIV-1 illness).

The pathogenetic factors that govern the severity and duration of acute illness at the time of seroconversion are unclear. A severe acute illness could be due to infection with HIV that escapes $CD8^+$ cell control and destroys $CD4^+$ cells because of a high level of replication [19, 20]. The $CD4^+$ cell count performed within 2 weeks of infection in 112 of our patients and the serum level of HIV RNA, determined for 30 patients (median time from the onset of acute illness, 17.0 days), both correlated with the CS ($CD4^+$ cell count: $r = -.20$, $P = .03$; HIV RNA serum level: $r = .44$, $P = .01$). These observations

Table 3. Risk of progression to category B disease, category C disease, and death by clinical score for 259 HIV-1-infected patients.

Clinical presentation (no. of patients)	Category B disease					Category C disease					Death				
	Median time* to disease in y (95% CI)	Percent of patients with disease			*P* value[†]	Median time* to disease in y (95% CI)	Percent of patients with disease			*P* value[†]	Median time* to death in y (95% CI)	Percent of patients who died			*P* value[†]
		At 3 y (95% CI)	At 5 y (95% CI)	At 7 y (95% CI)			At 3 y (95% CI)	At 5 y (95% CI)	At 7 y (95% CI)			At 3 y (95% CI)	At 5 y (95% CI)	At 7 y (95% CI)	
Asymptomatic (52)	7.1 (6.3–8.1)	11 (10–12)	23 (10–35)	49 (31–68)		7.6 (6.5–8.7)	2 (1–6)	18 (4–27)	37 (20–55)		8.2 (7.9–8.6)	0	9 (1–18)	17 (2–30)	
CS of 1–2 (77)	6.1 (5.2–7.0)	15 (6–24)	34 (20–48)	56 (39–74)		7.3 (7.0–9.2)	12 (4–21)	31 (16–46)	35 (19–50)		ND[‡]	3 (1–9)	13 (2–24)	37 (19–55)	
CS of 3–4 (102)	6.1 (4.3–7.8)	13 (6–20)	45 (28–62)	74 (54–93)		6.7 (3.9–9.5)	5 (1–10)	37 (20–54)	50 (31–69)		7.6 (5.7–9.5)	3 (1–8)	13 (2–24)	42 (23–61)	
CS of 5–6 (28)	2.8 (1.3–4.4)	52 (27–78)	81 (58–96)	100 (58–100)	.008	4.4 (3.2–5.5)	26 (4–29)	54 (26–82)	85 (58–100)	.03	5.5 (4.5–6.4)	13 (4–30)	23 (2–46)	77 (40–86)	.03

NOTE. CS = clinical score; ND = not determined.

* Cumulative progression to category B disease, category C disease, and death was determined by the Kaplan-Meier survival analysis.

[†] Generalized Wilcoxon test used to compare the survival distributions by clinical presentation.

[‡] Data not determined because <50% of patients presented with the event during the follow-up.

complement studies that reported a significant predictive value for a low $CD4^+$ cell count [5, 20] and a high viral load at 3–6 months following seroconversion [21]. Other factors, such as host genetics [22–24], HIV phenotype [25], cytotoxic immune response [26, 27], and HIV-1 dynamics [28], could affect the clinical expression of seroconversion and the subsequent prognosis. The $CD4^+$ cell count before seroconversion has been associated with the rate of disease progression [29]; in this study, patients with high $CD4^+$ cell counts before seroconversion tended to have high $CD4^+$ cell counts afterward, and their conditions progressed more slowly. Further investigations should explore in detail the effect of immunologic background on the spectrum of acute HIV-1 illness.

The oral cavity is an important target of HIV-1 infection. A diagnosis of acute HIV-1 infection is suggested by oral candidiasis and/or sore throat or pharyngitis associated with a skin rash and/or fever. Oral candidasis is a strong predictor of disease progression. Finally, the first category B disease occurred in the mouth in 64 patients (79%) (oral candidiasis, 55 patients; hairy leukoplakia, nine patients).

We must consider some limitations of this study. The results cannot be generalized to the whole population newly infected by HIV-1 because enrollment in the study cohorts was based on a voluntary decision. In addition, living far away from large cities and/or university medical centers can be a factor in the lack of recruitment of other symptomatic patients who have undergone HIV-1 seroconversion. Persons not considering themselves at risk of HIV-1 infection or less aware of their health status could be also underrepresented in the study population. Thus, these findings can be most appropriately compared with results provided for similar cohorts.

A limitation of our study is the heterogeneous population, since the patients were enrolled in different prospective studies with different inclusion criteria. We used complementary means to reduce this bias. A standardized form for collection of data was used at both centers. The standardized forms from each cohort study were double-checked with all private and hospital medical records available (231 of 259) by the same investigator (P.V.). However, diarrhea and pharyngitis were reported more frequently in Sydney ($P < .05$), and fever was reported more frequently in Geneva ($P < .05$). These differences could be related to the medical examination, the characteristics of the study population, a different presentation of acute HIV-1 illness by location, or a recall and/or misclassification bias. Nevertheless, all multivariate analyses were adjusted for the center (Geneva vs. Sydney) to account for these differences.

In some cases, the patients presented with clinical features that could also be considered as a clinical end point (see under Methods). This could be the case for oral candidiasis and diarrhea at the time of acute HIV-1 infection, which are also defining clinical events of category B disease. For the 81 patients who presented with a category B disease, the median duration of acute HIV-1 illness was 12.0 days (range, 4–62 days), and the median time from the onset of acute HIV-1 illness to category B disease was 1,281 days (range, 60–3,259 days). Two patients had progression to category B disease within 80 days. In both cases, the diagnosis of category B disease was oral candidiasis, and in one case, oral candidiasis was also reported at the time of acute HIV-1 infection. In this patient, oral candidiasis resolved by the 8th day after the onset of acute HIV-1 infection.

Fifty-five (68%) of 81 patients presented with oral candidiasis as a category B disease. Of these 81 patients, nine presented with oral candidiasis at the time of acute HIV-1 infection. We did not observe a statistical association between oral candidiasis at the time of acute HIV-1 infection and oral candidiasis as a category B disease ($P = .46$). Similar results were observed for the presence of esophageal candidiasis as a category C disease and the presence of oral candidiasis at the time of acute HIV-1 infection ($P = .70$).

The survival analyses could be biased because the time 0 determination was less accurate for the asymptomatic patients who underwent seroconversion. Symptomatic patients who underwent seroconversion, because of their symptoms, had an incentive to be retested sooner than they would have been had they remained asymptomatic, thus decreasing the average interval between the last negative test and the first positive test. To estimate this bias, we conducted a second survival analysis; asymptomatic patients were retested an average of 180 days after the previous (HIV-1-negative) test, and the symptomatic patients were retested an average of 140 days after the previous (HIV-1-negative) test. We assumed that if they had been symptomatic, the asymptomatic patients would have been tested an average of 40 days sooner than they in fact were. Therefore, we added 40 days to the follow-up of 65 symptomatic patients included on the basis of criterion 3. The results obtained after this survival calculation did not differ from the results reported in table 3 (data not shown). This result is in accord with the findings of Brookmeyer and Gail [30]; these investigators reported that the bias resulting from midpoint imputation in the case of doubly censured data is negligible when the period during which seroconversion occurred is <1 year, which was provided for in criterion 3.

Severely symptomatic patients who underwent seroconversion may have been followed up more closely, thus leading to earlier detection of outcomes (detection bias). This bias could lead to an overestimate of the difference between the sickest patients (CS = 5–6) and those with mild disease (CS = 0 or CS = 1–2). This bias is difficult to control for because even with a standardized 6-month follow-up, any complication occurring between medical examinations could be more accurately reported for severe events that required hospitalization. We do not know the quantity of medical resources used between each assessment, which could help estimate the likelihood of a detection bias having affected our results. Neverthe-

less, the various rates of disease progression by severity of acute HIV-1 illness that were observed in our study are compatible with available data on viral load and progression [31].

Finally, we limited the study to the symptoms and signs reported by >10% of patients as potential predictors. Univariate analysis showed that supraclavicular adenopathy (6 cases), esophagitis (4 cases), and encephalitis (3 cases) were associated with a faster disease progression (data not shown). However, we believe that these events are too uncommon at the time of primary HIV disease to be part of a prognostic CS, which we wanted to keep small and to be based on the most common symptoms possible.

In summary, the prognosis for symptomatic patients who underwent HIV-1 seroconversion varied. Oral candidiasis during acute HIV-1 infection was the sign most strongly associated with rapid disease progression. A dose-response relationship was found between the number of symptoms and signs reported at the time of acute HIV-1 illness and disease progression and death. The CS that we used could be a helpful clinical tool in determining prognosis and in deciding about the early use of therapy when viral load determinations are not available. Patients at greatest risk of progression should be monitored closely, because they are more likely to require antiretroviral and prophylactic therapies and would have more to gain from the early initiation of treatment [15, 32].

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